region 4 corresponds to the domain of the variable region from amino acids 103 to the end of the variable region. The framework regions for the light chain are similarly separated by each of the light claim variable region CDRs. Similarly, using the definition of CDRs by Chothia et al. or McCallum et al. the framework region boundaries are separated by the respective CDR termini as described above.

As used herein,the term "donor" is intended to mean a parent antibody molecule or fragment thereof from which a portion is derived from, given or contributes to another antibody molecule or fragment thereof so as to confer either a structural or functional characteristic of the parent molecule onto the receiving molecule. For the specific example of CDR grafting, the parent molecule from which the grafted CDRs are derived is a donor molecule. The donor CDRs confer binding affinity of the parent molecule onto the receiving molecule. It should be understood that a donor molecule does not have to be from a different species as the receiving molecule of fragment thereof. Instead, it is sufficient that the donor is a separate and distinct molecule.

As used herein, the term "acceptor" is intended to mean an antibody molecule or fragment thereof which is to receive the donated portion from the parent or donor antibody molecule or fragment thereof. An acceptor antibody molecule or fragment thereof is therefore imparted with the structural or functional characteristic of the donated portion of the parent molecule. For the specific example of CDR grafting, the receiving molecule for which the CDRs are grafted is an acceptor molecule. The acceptor antibody molecule or fragment is imparted with the binding affinity of the donor CDRs or parent

molecule. As with a donor molecule, it is understood that an acceptor molecule does not have to be from a different species as the donor.

A "variable region" when used in reference to an antibody or a heavy or light chain thereof is intended to mean the amino terminal portion of an antibody which confers antigen binding onto the molecule and which is not the constant region. The term is intended to include functional fragments thereof which maintain some of all of the binding function of the whole variable region. Therefore, the term "heteromeric variable region binding fragments" is intended to mean at least one heavy chain variable region and at least one light chain variable regions or functional fragments thereof assembled into a heteromeric complex. Heteromeric variable region binding fragments include, for example, functional fragments such as Fab, $F(ab)_2$, Fv, single chain Fv (scFv) and the like. Such functional fragments are well known to those skilled in the art. Accordingly, the use of these terms in describing functional fragments of a heteromeric variable region is intended to correspond to the definitions well known to those skilled in the art. Such terms are described in, for example, Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, New York (1989); Molec. Biology and Biotechnology: A Comprehensive Desk Reference (Myers, R.A. (ed.), New York: VCH Publisher, Inc.); Huston et al., Cell Biophysics, 22:189-224 (1993); Plückthun and Skerra, Meth. Enzymol., 178:497-515 (1989) and in Day, E.D., Advanced Immunochemistry, Second Ed., Wiley-Liss, Inc., New York, NY (1990).

As used herein, the term "population" is intended to refer to a group of two or more different

molecules. A population can be as large as the number of individual molecules currently available to the user or able to be made by one skilled in the art. Populations can be as small as 2-4 molecules or as large as 10^{13} molecules. An example where a small population can be useful is where one wishes to optimize binding affinity of a variable region or of heteromeric binding fragments by compiling beneficial differences from a small number of parent molecules having similar binding affinity into a single variable binding fragment species. An example of where large populations, including as large as 10^{8} or greater different molecules, can be desired is where all possible combinations of amino acids differences between donor and acceptor at all positions within a variable region are to be generated in order to obtain maximum diversity and increase the efficiency of compiling beneficial changes. In some embodiments, populations are between about 5 and 10 different species as well as up to hundreds or thousands of different species. The populations can be diverse or redundant depending on the intent and needs of the user. Those skilled in the art will know what size and diversity of a population is suitable for a particular application.

As used herein, the term "altered" when used in reference to an antibody variable region is intended to mean a heavy or light chain variable region that contains one or more amino acid changes in a framework region, a CDR or both compared to the parent amino acid sequence at the changed position. Where an altered variable region is derived from or composed of different donor and acceptor regions, the changed amino acid residues within the altered species are to be compared to their respective amino acid positions within the parent donor and acceptor regions. For example, a variable region